

1158

EVALUATION OF THE POTENCY OF ANTIBODY DRUG CONJUGATE-FREE DRUGS ON INNATE IMMUNE CELLSClaire Stoffers*, Katie Snead, Ryan A Heiser, Alyson J Smith. *Seagen, Bothell, WA, USA*

Background Antibody drug conjugates (ADCs), that pair highly cytotoxic drugs with a tumor targeting antibody, have become a mainstay of many cancer treatment paradigms. Currently approved ADCs utilize payloads that disrupt tubulin (including monomethyl auristatins (MMAE and MMAF), inhibit topoisomerase 1 (DXd and SN-38) or induce DNA cleavage (ozogamicin). Primarily these drugs have been studied for their direct cytotoxic effects on tumor cells, but many are highly permeable and have the potential to affect other intra-tumoral cells, including immune cells. These effects could adversely impact anti-tumor immunity and/or synergy with immunotherapies, but to date has been under studied.

Methods To determine how these various free drugs effect immune cells within a tumor microenvironment we compared the sensitivity of various innate immune cells (peripheral NK cells, IL2/IL15 expanded and activated NK cells, in vitro derived macrophages in various polarization states (M0, M1, TAM) and myeloid derived suppressor cells (MDSC)) to killing directed by tubulin disruptor payloads (MMAE, MMAF) various camptothecin (CPTs) topoisomerase 1 inhibiting payloads or a highly potent DNA crosslinking payload pyrrolo-benzodiazepine (PBD). We assessed how payload treatment effects hallmark innate immune activities of these cells. For macrophages, we queried how payloads changed the ability to respond to LPS challenge and for MDSC we assessed ability to suppress T cell proliferation after CD3/28 stimulation. Induction of cytokine production directly from tumor cells in response to payloads was also assessed.

Results The PBD compound proved to be highly cytotoxic to all cell types, while MMAF generally did not demonstrate cytotoxicity to any of the cells tested, likely due to the low permeability of the drug. Innate immune cells demonstrated differential sensitivity to killing by the CPTs vs. MMAE. Activated NK cells showed the highest sensitivity, followed by peripheral NK cells and then MDSCs, with the least sensitive being macrophages. Generally, all cell types were more sensitive to killing by CPTs than MMAE. When evaluating activity, pre-treatment with MMAE unexpectedly drove increased macrophage activation while CPT treatment resulted in decreased activation. For MDSCs, it was noted that pre-treatment with certain payloads caused less suppression of activated T cells. And finally, robust cytokine induction was observed from several tumor cell lines that was quite varied based on payload used and cell line.

Conclusions These data begin to elucidate the effects of various ADC payloads on intratumoral bystander innate immune cells and expand our understanding of the wider effects of ADCs on the tumor microenvironment.

Acknowledgements We would like to acknowledge Ryan Lyski, Joe Hamilton, Philip Moquist and Svetlana Doronina for their provision of study materials and chemical insight.

<http://dx.doi.org/10.1136/jitc-2023-SITC2023.1158>